Review

Mutated Genes in Pancreatic Cancer

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ABSTRACT

Pancreatic cancer continues to be a deadly malignancy with still high mortality and poor survival. Little progress has been made on the treatment of advanced pancreatic cancer despite the significant advances in understanding, diagnosis, and access to conventional and novel treatments. Molecular pathology of the lesion is the key of our understanding of the mechanisms underlying the development of this cancer and will probably help us in earlier diagnosis and better therapeutic results. New treatment strategies and a more careful evaluation of innovative therapies are clearly needed for this disease. In view of many findings pancreatic cancer should be regarded as a systemic disease, and over the last several years, investigators have gained a better understanding of the molecular biology and events that lead to the development of malignancies. We here review the novel developments in the systemic exploring for commonly mutated genes in pancreatic cancer.

Key words: Pancreatic cancer; Epithelial growth factor; Matrix metalloproteinases; Oncogenes

INTRODUCTION

Pancreatic cancer (PC) is one of the most lethal cancers worldwide, as indicated by its mortality incidence ratio of 98%[1]. The prognosis for pancreatic cancer is extremely poor, and the high mortality can be attributed to the ambiguous symptoms, a distinct lack of early diagnostic methods and a lack of effective therapy[2]. Surgery remains the only curative treatment option for this disease but 80% of pancreatic cancer patients have unresectable or metastatic disease[3,4]. Moreover, adjuvant chemotherapy or radiotherapy was assessed in several trials in order to improve patients' prognosis[5,6]. Thus, most patients receive palliative treatment with the aim of an improved quality of life.

In view of many findings pancreatic cancer should be regarded as a systemic disease, and over the past few decades, knowledge of the genetic defects involved in tumor formation and growth has increased rapidly. There is an imperative need of analyzing and understanding the primitive lesions that lead to invasive pancreatic cancer. Identification of cancer escape mechanisms and critical cell survival pathways has launched the development of novel antitumor agents. This review will focus on the recent developments in the systemic exploring for commonly mutated genes in pancreatic cancer.

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K-ras

K-ras activation is known to contribute to cancer cell survival in a number of different tumor types and experimental systems. In mouse models of cancer, somatic activation of oncogenic K-ras is necessary for the early onset of tumors, and its continuous production is necessary for the maintenance of tumor viability[7]. Molecular genetic analysis has identified that activating K-ras mutations, as the earliest and most common genetic mutations in pancreas cell transformation and tumor progression, are found not only in 70% to 95% of pancreatic carcinoma tissues but also in pancreatic juice, fine-needle aspirations of

the pancreas, duodenal fluid, and blood and stool of pancreatic cancer patients[8,9]. Recent study demonstrated that the introduction of a promoterless full-length K-ras cDNA could efficiently suppress endogenous K-ras gene expression in human pancreatic cancer cells. This inhibition was achieved when the adequate levels of the responsible effectors were reached. Knockdown of K-ras expression in pancreatic cancer cells resulted in slower cell proliferation and lower tumorigencity in mice[10]. Moreover, K-ras mutations have been reported as a negative prognostic factor after surgery and adjuvant chemoradiation in pancreatic cancer[11,12].

p53

In human cancers, the most frequent mutant gene is p53, which has a central position in cell cycle regulation through its role in inactivating a variety of genes and interrupting cell proliferation at G1/S checkpoint. p53 mutations cause loss of the above functions and are central in carcinogenesis leading to uncontrolled cell growth and proliferation, increased cellular survival and chromosomal instability. It has been reported that p53 mutations are found in up to 76% in pancreatic cancer[13,14]. Usually, mutations of p53 are not specific but rather sporadic and are resulting in the production of a mutant p53 protein which lives longer than the wild type(normal) p53 protein. Furthermore, p53 mutations may lead to resistance to chemotherapy treatments due to impaired p53-induced apoptosis[15]. There is emerging evidence that the oncogenic potential of human and/or murine double minute-2 protein(hdm2)stems not only from its ability to counteract tumor suppressor p53 but also from its less understood p53-independent functions. Sui X et al concluded from their results that hdm2 is expressed in pancreatic cancer cells as a result of activated Ras signaling, and that it regulates cellular proliferation and the expression of three novel target genes by p53-independent mechanisms[16]. However, whether these mutations have also a prognostic significance remains unclear. Few researchers have suggested a shorter overall survival in pancreatic cancer patients carrying p53 mutation compared to p53(-) patients[13,17].

p16

Mutation and loss of p16 activity results in absence of the inhibitory effects at the level of cyclin D-CDK4 interaction, thereby promoting cell cycle progression. Genetic alterations of this locus through gene mutation, deletion, or promoter hypermethylation are found in 80% to 95% of sporadic pancreatic cancers[18]. Genetic analyses have shown that p16 alterations are very common in pancreatic adenocarcinomas but these alterations are not necessarily seen in cultured cell lines. Moreover, loss of p16 expression could be correlated with less differentiated tumors, shorter overall survival, and the presence of metastatic disease[19,20]. The polymorphic genotypes of the p16 gene were associated with significantly shorter time to tumor progression and poorer response to therapy in pancreatic cancer[21]. Functional inactivation of the tumour suppressor p16 marks a key event in pancreatic carcinogenesis. Conversely, reconstitution of the biological action of p16 provides an attractive therapeutic approach. Schulz P et al addressed the consequences of p16 re-expression in MiaPaca-2 pancreatic cancer cells in vivo in the orthotopic tissue context. They found p16 capable of reducing primary tumor growth. In addition, p16 restitution resulted in a marked reduction of tumor angiogenesis, largely accounted for by a p16-dependent inhibition of lymphangio-genesis[21].

DPC4/SMAD4

Another tumor suppressor gene which is involved in pancreatic cancer pathogenesis is the DPC4 gene also known as SMAD4. In normal cells the product of this gene plays a role in TGF-β mediated signal transduction, gene transcription and growth arrest[22]. Inactivation of DPC4 facilitates uncontrolled cellular growth and proliferation. It is found that about 50% of pancreatic cancers present mutant genes[24]. Loss of the DPC4 expression is a rather late event in the pathogenesis of pancreatic cancer, as this gene was expressed normally in PanIN1 and 2 and only in 30% of cases with PanIN3[23,24]. Cao D et al utilized the Gene Logic Inc. BioExpress™ platform and Affymetrix U133 GeneChip® set to determine the changes in gene expression associated with SMAD4 gene inactivation in a series of well-characterized pancreatic cancer cell lines to define the downstream effects associated with SMAD4 gene inactivation, which offers insight into the role played by SMAD4 in pancreatic cancer, as well as providing potential novel targets for the development of molecular therapeutics in pancreatic cancer[25]. Pancreatic cancers are represented by distinct genetic subtypes with significantly different patterns of failure. Determinations of DPC4 status at initial diagnosis may be of value in stratifying patients into treatment regimens related to local control versus systemic therapy[26]. Whether the DPC4 status has a prognostic value remains controversial, as in a few studies positive DPC4 status was associated with better outcome and survival post resection[25,27],